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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,096	GADDAM ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,7,9 and 11-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,3,5,7,9,11-19 and 64* is/are allowed.

6)☒ Claim(s) *20-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3/04&9/0* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to remarks filed on 3/31/04. Applicant has not amended any claims. There are fifty-nine claims pending and fifty-nine under consideration. Claims 1, 2, and 11 are compound claims. Claims 12-23 are composition claims. Claims 24-63 are use claims. Claims 3, 5, 7, 9, and 64 are synthesis claims. This is the third action on the merits. The application concerns some salts of phenoxazine and phenothiazine compounds, compositions, synthesis, and uses thereof.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30-35 and 52-55 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 30-35 and 52-55 recites the limitation "dementia", "cancer", and "inflammation" in lines 7 and 9. There is no antecedent basis for this limitation in parent claim 24, which recites "diseases in which insulin resistance is the underlying pathophysiological mechanism". Applicants have not asserted and it is not art recognized that the three rejected diseases are so mechanistically related.

Applicants make three arguments concerning this rejection. Firstly, they state that they have asserted that there is a mechanistic relationship. Secondly, they allege that, "that cancer, dementia and inflammation are related to insulin resistance". Thirdly, they cite eight papers and news articles to establish the questioned relationship. These are not persuasive. While Applicants have made such an assertion in their remarks, there is no such assertion in the specification. Applicants' remarks are not evidence and the assertion is absurd on its face. Secondly, the claims do not require a mere relationship between the rejected diseases and insulin resistance. The claims require that " insulin resistance is the underlying pathophysiological mechanism". This is a much larger hurdle than merely establishing a relationship among the conditions. What if cancer indirectly caused insulin resistance? That would be a relationship between the two, but not the causal relationship required by the claim language.

Thirdly, concerning the cited references a complete review of these references fails to reveal any use of any insulin-like substance to treat any disease. Applicants fail to point to any specific passages in these numerous and lengthy references that support this alleged clinical correlation. All are completely speculative, lacking any clinical data what so ever. None concern the entire broad scope of cancer, inflammation, or dementia, instead discussing only narrow

specific examples of such diseases. Only the abstract of Watson (CNS Drugs) was provided. Nowhere does this reference state that insulin resistance causes Alzheimer's disease. In fact in the first sentence implies that insulin resistance is a consequence of Alzheimer's disease. In any case both conditions are associated with aging, so removal of the age factor would be required before even a statistical linkage between these two conditions could be established. Messier (Beh. Brain Res.) reviews the effect of glucose, not insulin, upon memory in Alzheimer's' patients, does not state which is the cause or which is the effect, or even rule out that these are coincidental effects. No Author (Clinician Reviews) discusses diabetes and Alzheimer's disease. Diabetes is not insulin resistance. No Author (Clinician Reviews) states, "[r]egarding the dramatic increase in dementia seen in patients taking insulin, Dr. Lovestone suspects that the action of insulin itself insulin signaling, the regulation of glucose metabolism, or neuronal insulin receptor resistance may be contributing factors." Thus, insulin, not insulin resistance may be the causative factor. In any case, suspicion is not the level of proof required. Kuusisto (Brit. Med. J.) concludes that, "[f]eatures of the insulin resistance syndrome are associated with Alzheimer's disease" and that association is unrelated to the apolipoprotein process of Alzheimer's. Associated does not mean that insulin resistance causes Alzheimer's disease. In fact, the way it is stated

in the paper, insulin resistance might be caused by Alzheimer's disease. Applicants claim requires that insulin resistance cause Alzheimer's disease, not the other way around.

Applicants supplied only the first page of Isaksson (Pancreatology). This article concludes that pancreatic cancer induces "disturbance in glucose metabolism that accompany patients with pancreatic cancer". That is the opposite relationship implied by Applicants' claim language. Applicants failed to supply the primary sources upon which Baker (Buffalo Reporter) was based. Baker (Buffalo Reporter) writes "[u]niversity researchers have confirmed a significant link between breast-cancer risk and physical characteristics of insulin resistance and higher-than-normal male and female sex hormones in a woman's bloodstream". There are three factors associated here, a relationship between hormones and breast cancer, and a relationship between hormones and insulin resistance. Where is the relationship between breast cancer and insulin resistance stated? What is that relationship, cause and effect or something else?

Applicants failed to supply the primary sources upon which Merkin (Report) was based. It states "[a] recent report from Harvard Medical School shows that both diabetes and colon cancer can be caused by insulin resistance". The relationship between diabetes and insulin resistance is not relevant here. The

purported relationship to colon cancer would hardly be conclusive for all thousands of different cancers and no one has been able to substantiate this report in the nine years since it was published. Only an abstract to Hsing (J. Nat. Cancer Institute) was provided and Applicants cut off the right side of this document. In a follow-up study, Stattin (Journal of the National Cancer Institute) contradicted the report of Hsing (J. Nat. Cancer Institute) stating in the first paragraph, second column,

> (QUICKI), and we found no association between these indices or insulin levels and prostate cancer risk (Table 1). Given

Only an abstract to Fetsa (Circulation) was provided and again Applicants cut off the right side of this document. Fetsa (Circulation) reports "correlation" of C-reactive protein (CRP), fibrinogen, and white cell count to insulin resistance syndrome. "Correlation" is not the causal relationship required by the plain meaning of Applicants' claim language and the three clinical markers discussed are hardly indicative of all "inflammations", again required by Applicants claim language.

Finally, in the previous office action, the Examiner asked four specific questions concerning Applicants alleged causal relationship. Applicants declined to answer any of the four questions.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-63 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating type II diabetes, insulin resistance, and hypercholesteremia, does not reasonably provide enablement for treating the multitude of unrelated diseases embraced. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The issues are the breadth of the claims, the narrow scope of data present, and the lack of correlation between clinical efficacy and the assays employed by the Applicants.

a) Determining if any particular claimed compound would treat any particular PPARα or PPARγ related disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large quantity of experimentation. b) The direction concerning treating diseases is found in paragraph 104, spanning pages 17 to 18, which merely states Applicants' intention to do so. Applicants describe formulations in paragraphs 106 to 112, spanning pages 18 to 21. Two prophetic examples of the formulations required to practice Applicants intended therapies are reported. Doses required to practice their invention are described in paragraph 113, page 21. A 10,000-fold range of doses is recommended. The thiazolidedione compounds troglitazone, rosiglitazone, and pioglitazone are the only PPARγ antagonists ever used to treat any human disease. These compounds are structurally unrelated to those of Applicants. No PPARα agonist has ever shown clinical efficacy in human disease therapy. How then is the skilled physician to know what dose of Applicants' compounds to use for each of these dozen different diseases? There are two PPARα or PPARγ receptor binding *in vitro* assays described in paragraphs 192-213, spanning pages 36-42. There is data for six of Applicants' compounds. It

is unclear if these two assays are correlated to clinical efficacy for any disease treatment. It is also not possible to conclude if Applicants compounds are agonists or antagonists at these receptor sites. Antagonists, would of course exacerbate, the pathological conditions that Applicants intended to treat. There is an *in vivo* cholesterol-lowering assay in the rat reported. Only one of Applicants' compounds has been tested in this assay. There is a prophetic HMGCo enzyme assay and there are three prophetic diabetes, cholesterol lowering in the mouse, and obesity assays also described. None of Applicants compounds appear to have been tested for these therapeutic indications.

c) There is no working example of treatment of any disease in man. There is one compound tested for hypercholesteremia in the rat. d) The nature of the invention is clinical treatment of disease with PPARα or PPARγ antagonists, which involves physiological activity. e) The state of the clinical arts in PPARα or PPARγ related diseases is provided by Cobb (Ann. Reports Med. Chem.) that antidiabeteic efficacy has been correlated to affinity to the PPARγ binding site, in the first paragraph, page 216. Sapone (Pharmacogenetics) reports that mice lacking any PPARα receptors develop normally. In his abstract he says that "[t]he biological significance of these novel PPARalpha alleles remains to be established".

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the thousands of compounds of claim 1 as well as the dozens of claimed diseases. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Applicants offer four arguments concerning the enablement rejection. Firstly, they dispute the quantity of experimentation required to practice the clinical claims, asserting, "[t]he steps that the examiner has outlined are not required for meeting the enablement requirement in a patent application". The Examiner stated that either this clinical experimentation or data from an art-recognized model was required. Neither is present here. If this is not the

experimentation required, then what is? Applicants do not dispute that whatever experimentation is required, the quantity of that experimentation is large.

Secondly, Applicants assert, "[t]here is no requirement that a patent application include a working example and no requirement that an application include in vivo data and especially not human data." The Applicants do not dispute that no working example is present. That lack is merely one of eight factual components leading to a conclusion of undue experimentation. Applicants are reminded of MPEP §2164.02 "[l]ack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art". The clinical arts are unpredictable. The Examiner made no requirement that clinical data be produced, although that is certainly one way to provide enablement. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

Thirdly, Applicants state that FDA approval cost $25,000,000 and the lack of clinical data cannot be the basis of an enablement rejection. In fact, the last number the Examiner has heard for approval was $750,000,000. The lack of human data was not the basis of the rejection and the Examiner made no requirement that such data be present. Clinical data is certainly one way to provide

enablement. Rather the evidence as a whole and all eight Wands factors were considered again before reaching a conclusion of non-enablement.

Fourthly, Applicants state that " it is extremely unlikely that a physician with a MD degree would recommend that a patient use a compound of formula (1) according to any one of claims without the compound having been approved by the US FDA". Applicants do not dispute the artisan using the invention would be a physician. The Examiner agrees with Applicants' assertion but requests clarification to the relevance of this to the enablement analysis performed above. To which factor is this relevant?

Allowable Subject Matter

4. Claims 1, 3, 5, 7, 9, 11-19, and 64 remain allowed.

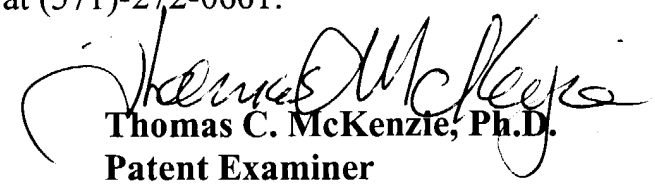
Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date

of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

7. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.



Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

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